

REVIEW ARTICLE

Managing a child with possible allergy to vaccine

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Abstract

Similarly to other medications, vaccines may be responsible for allergic reactions. Although IgE-mediated allergies to vaccine are extremely rare, they are clearly overdiagnosed. Indeed, accurate diagnosis of vaccine allergy is important not only to prevent serious or even life-threatening reactions, but also to avoid unnecessary vaccine restriction. Systematic approaches have been proposed and, if implemented, will likely reduce the number of children being inappropriately labeled as allergic to vaccine. In diagnosis of vaccine allergy, the patient's history is central although not sufficient. In case of suspicion of an allergy, the child should be referred to an allergist in order to perform a complete allergy workup, based primarily on skin tests and/or specific IgE. Highlighting the most recent literature, this article will address the management of children with a possible allergy to vaccine.

Clinical case

A girl aged 10 yr received her fourth dose of diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine intramuscularly. Five hours later, she developed a large reaction (induration, redness, and swelling) at the injection site, associated with substantial pain and itching. She was treated with cold packs and oral antihistamines. The acute symptoms disappeared within few days, whereas the parents described a firm painless nodule persisting for 1 month. She neither had a history of food or drug allergy nor previous adverse events after vaccinations. In the allergy workup, a patch test to aluminum was positive. The parents were told to avoid aluminum-containing products, particularly antiperspirants and deodorants. One year later, based on measurement of antibody titers, an additional dose of DTaP vaccine was required. At that time, a vaccine without aluminum was not available, and she received the same DTaP vaccine containing aluminum. According to recommendations, the injection was administered intramuscularly, and she tolerated the vaccination with only a mild local reaction lasting only 24 h, without any other symptoms.

Introduction

Since coming into widespread use, routine immunization has been shown to be one of the most cost-effective methods of all health interventions, significantly reducing morbidity and saving countless lives. Approximately 20 vaccines are currently in use, and each year billions of doses are administered worldwide (1). Similar to any other medication, vaccines may be responsible for adverse reactions, ranging from mild local reactions to fatal outcomes. The rate of reported vaccine-induced adverse events is low and ranges between 3 and 83 per 100,000 vaccine doses of the most frequently used vaccines, according to worldwide post-marketing surveillance data (2–5).

Due to the large number of administrations, vaccines have even been reported to be the most common cause of adverse drug reactions in children, and concerns about possible allergic reactions to vaccines are frequently raised by both patients/parents and healthcare providers (6, 7). On the other hand, true hypersensitivity reactions to vaccines are extremely rare with the number of confirmed reactions being very low, that is, 1–3 per million vaccine doses according to some estimates (8, 9). This discrepancy is mostly due to the fact that patients experiencing

any reaction occurring in temporal (but not necessarily causal) relationship to vaccination often label themselves as being allergic. Indeed, many adverse events to vaccines can hint at the possibility of allergy. Nevertheless, the term 'allergy' refers only to immunologic reactions, either antibody-mediated or cell-mediated, and should be clearly distinguished from other adverse reactions with no proven immunologic mechanism. The latter may be more broadly described as 'hypersensitivity', that is, unexpected objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons (10). From a medical point of view, diagnosis of allergy to vaccines is difficult, and occurrence of some adverse reactions after immunization may result in labeling a child as allergic due to the lack of a better explanation of the event. Subsequently, although crucial, it is very difficult for clinicians to design a safe immunization plan for children with suspected, but unproven, allergy. The economic burden and the impact on health, both from an individual point of view and in terms of public health, are very important. Therefore, the proper identification, evaluation, and management of patients with a suspected vaccine allergy are essential. Systematic approaches have been proposed and, if implemented, will likely reduce the number of unvaccinated children.

In this article, we will discuss adverse reactions to vaccines consistent with hypersensitivity as well as their clinical manifestations and the major constituents in vaccines that may elicit these reactions. Finally, we will make suggestions for the management of children with suspicion of allergy to vaccine such as the one presented in the clinical case, including a detailed algorithm.

Clinical manifestations of hypersensitivity reactions to vaccines

Hypersensitivity reactions represent only a small proportion of all adverse reactions associated with vaccine administration. From a practical perspective, hypersensitivity reactions following immunization should be classified according to the extent (local, systemic) and the timing of the reaction (immediate, non-immediate) (11, 12). The frequency (common, rare) and severity (minor, moderate, major) of the reaction should also be taken into account.

Local reactions

Tissue damage by the puncture itself as well as the injection of foreign material into tissues is responsible for a non-specific inflammatory reaction of the skin, leading to mild local reactions. Of note, the length of needle may play a role as recent evidence has shown that reactogenicity is dramatically reduced with correct needle length, longer needles being associated with a lower rate of local reactions (13–15). Larger local reactions are less common but can occur with a large number of vaccines, particularly those containing toxoids and/or adjuvants (16). The pathogenesis of these reactions is complex, probably multifactorial and not fully understood. Among large local reactions, two different general patterns have been described. First, typical large local reactions to

vaccines include pain, swelling, and redness at the injection site, suggesting an important underlying inflammation. Some investigators have suggested that these large local reactions occurring typically within 24–72 h after vaccination are the result of an antigen/adjuvant Toll Like Receptor (TLR)-induced inflammation and/or an antibody-mediated Arthus-type reaction (16–22). The latter is characterized by residual antibodies still present in the host due to previous sensitization (23). The rate of local reactions has been shown to be higher after receiving multiple doses of certain vaccines, even though shorter intervals between vaccines administration have not been associated with a higher rate of local reactions (24, 25). The second clinical pattern arises within 24 h after vaccination and is typically not associated with pain, reduction in limb movement, local redness, or systemic symptoms such as fever. In this case, the reaction resembles a benign reactive edema (26), thus suggesting extravasation mechanisms still poorly understood (27, 28). The term 'extensive limb swelling (ELS)' is used when edema extends at least to the elbow or knee of a vaccinated extremity (16). In either cases, large local reactions subside spontaneously without sequelae (22) and recall injections are well tolerated (29), especially when performed sequentially with mono or polyvalent vaccines (30, 31). Of note, these local reactions can be observed during the first injection (22).

Local reactions in the form of subcutaneous nodules can occur, especially after the injection of vaccines containing aluminum salts. Eczema at the injection site has also been described after administration of vaccines containing aluminum hydroxide, thimerosal, or formaldehyde (32–34). These reactions have been reported mainly in adults and are rarely encountered in children. They may occasionally extend beyond the injection area or may even become generalized (35–37). Importantly and as shown in the clinical case, none of the different types of local reaction should be considered as a contraindication to further vaccination.

Systemic reactions

Systemic reactions are reported in approximately 5–13% of the patients being vaccinated (38). The most frequent clinical manifestations include fever, irritability, drowsiness, and rash (39). Most of these systemic reactions result from non-specific mechanisms and do not relapse during booster shots. From a clinical point of view, it is important to distinguish between immediate reactions (IgE-mediated), which usually occur within minutes to hours following vaccination, and non-immediate reactions (non-IgE-mediated), the time of onset ranging between a few hours to several days. Immediate reactions are characterized by various combinations of IgE-mediated symptoms, that is, urticaria and/or angioedema, rhinitis, wheezing, and hypotension. Although rare [i.e. 1–3 reactions per million vaccine doses (8, 9)], identification of these reactions is important because they carry the risk of life-threatening anaphylaxis if the patient is re-exposed. Regarding non-immediate reactions, the most common clinical manifestations include maculopapular rash, delayed onset urticaria, and erythema multiforme. Other immunologic reactions (serum sickness-like disease, Henoch Schonlein Purpura,

specific organ damages, etc....) are even rarer and are not discussed in this article.

Potential allergens contained in vaccines

Bohlke et al. (9) reviewed 657 potential adverse drug reactions and identified five cases of potentially vaccine-associated anaphylaxis after administration of 7,644,049 vaccine doses, for a risk of 0.65 cases/million doses. Although being extremely rare, anaphylactic reactions to the microbial components of the vaccines themselves have been reported (40–46). One of the most well-known examples is anaphylaxis after a tetanus–diphtheria booster, confirmed by positive skin tests and specific IgE to both tetanus and diphtheria toxoids (40, 47–49). In addition to microbial antigens, vaccines contain residual components of the culture medium, preservatives, or stabilizers, which may rarely elicit hypersensitivity reactions in susceptible individuals.

Gelatin

Gelatin is a protein derived from collagen and is added as a stabilizer in many vaccines. Although extremely rare, gelatin may be responsible for anaphylactic reactions after administration of measles, mumps, and rubella (MMR), varicella, Japanese encephalitis, rabies, and some influenza vaccines (50–53). Of note, the content of gelatin is highly variable between different vaccines, ranging from 30 to 15,500 µg per dose (54, 110). A genetic predisposition to gelatin allergy has been suggested by the demonstration of a strong association between gelatin allergy and HLA-DR9, which is particularly prevalent in Japan (55, 56). Specific measures (i.e. removal of gelatin from certain vaccines and used of more hydrolyzed gelatin in others) lead to a significant reduction of vaccine-induced anaphylaxis (57). These anaphylactic reactions due to gelatin can be confirmed by positive skin tests and/or specific IgE (58). Gelatin-adsorbed vaccines can also be responsible for non-immediate reactions (59).

In addition, gelatin is a common ingredient in processed foods, particularly in candies and desserts. Preexisting history of

food allergy to gelatin has been subsequently found in several patients reacting to vaccine. From another point of view, vaccination might trigger a later onset of food allergic reactions to gelatin in some children (60). Patients who have experienced anaphylaxis after ingestion of gelatin should be evaluated by an allergist prior to receiving a gelatin-containing vaccine (52, 58, 60–63). Symptomless consumption of gelatin should of course not exclude an allergy to gelatin, as other routes of sensitization have been incriminated, particularly through gelatin-containing vaccines (58, 60). Gelatins used in medical applications are almost exclusively derived from cows and pigs and are highly cross-reactive (52, 64, 65). Thus, patients sensitized to pork or beef are at higher risk of reaction to these gelatins, and caution should be taken when administering gelatin-containing vaccines (65). Recently, gelatin anaphylaxis has been associated with an allergy to red meat and with sensitization to the carbohydrate galactose- α -1,3-galactose (66).

Hen's egg proteins

Concern has existed over administration of vaccines prepared on embryonated chicken eggs (i.e. rabies, yellow fever, tick-borne encephalitis and influenza vaccine) to egg-allergic patients. Indeed, small amount of egg proteins that can be found in these vaccines lead to a potential risk of inducing an allergic reaction when administered to an individual with egg allergy. The vaccine with the highest amount of residual egg proteins (micrograms) is that to yellow fever (Table 1). Regarding influenza vaccines, changes in that safety issue have recently occurred. Indeed, the ovalbumin content of recent vaccines has been shown to be very low, <1 µg per 0.5 ml dose (67–73). Several recent studies including a total of several thousand patients have shown that influenza vaccine can be safely administered, even to patients with severe egg allergy (see section 'Egg-allergic patients and vaccination') (68–77). Regarding MMR vaccines, those are produced on chicken embryo fibroblasts (not actually in eggs cultures) and contain negligible or no egg proteins (78, 79). As demonstrated by several large studies, there is therefore no contraindication to vaccinate egg-allergic children with MMR vaccine without prior skin testing

Table 1 Egg content of vaccines and managements of egg-allergic patients (134). Adapted with permission from: Kelso, JM. Allergic reactions to vaccines. In: UpToDate, Basow DS (Ed), UpToDate, Waltham, MA 2013. Copyright © 2013 UpToDate, Inc. For more information visit www.uptodate.com

Vaccine	Grown in	Egg protein content	Approach in egg-allergic patients
Measles and mumps	Chick embryo fibroblast cell cultures	Picograms to nanograms	Administer in usual manner
Purified chick embryo rabies	Chick embryo fibroblast cell cultures	Picograms to nanograms	Administer in usual manner
Influenza (killed injected vaccines [†])	Chick extra-embryonic allantoic fluid	Micrograms	In case of mild egg allergy, administer in usual manner in general practitioner office and follow-up after 30 min In case of severe egg allergy, administer in allergist office and follow-up after 30 min
Yellow fever	Chick embryos	Micrograms	Skin test with vaccine prior to administration

[†]Egg proteins content <1 µg per 0.5 ml dose.

(80, 81). Chicken proteins can also be found in some vaccines (i.e. yellow fever vaccine) and may be responsible for reactions in patients with a true allergy to chicken.

Preservatives and adjuvants

Aluminum

Some vaccination agents lead to an insufficient immune response and require an adjuvant (82). Aluminum has been shown to be efficient to hasten antivaccinal humoral immunity and is therefore added in a wide range of vaccines. Persistent itching, subcutaneous nodules, or granulomas at the injection site after vaccination with aluminum-adsorbed vaccines have been described in several reports, but it is considered to be a rare event (83–89). The condition tends to be transient but can sometimes persist for a few weeks or even years. Hyper- and hypopigmentation, hypertrichosis, and lichenification have been associated with such nodules (85). In rare cases, these nodules become inflammatory and even turn into an aseptic abscess (90). Contact allergy to aluminum as demonstrated by positive patch tests in individuals with persistent itching nodules has been reported since the 1980s (84, 85, 87, 88, 91–97). However, it is believed that the majority of these nodules result from an inflammatory foreign body reaction, and their frequency and intensity are dependent of the dose of aluminum hydroxide present in the vaccine (98). In aluminum-sensitized patients requiring a vaccine containing aluminum, the injection should be administered deep enough as intramuscular administration may prevent the formation of granulomas (82, 97). Some patients with sensitization to aluminum can develop contact dermatitis, either localized or generalized, after vaccine administration (33). These reactions can occur despite absence of known exposures to aluminum-containing products.

Thimerosal, phenoxyethanol, and formaldehyde

These preservatives are added to a large variety of vaccines and may be responsible for allergic reactions. Thimerosal has been shown to be one of the most effective preservative, improving vaccine stability, potency, and safety. However, it has been less used over the last decades in childhood vaccines, as a precautionary measure due to its mercury content (99). Thimerosal has not been clearly documented to cause immediate hypersensitivity reactions to vaccines, but it has been incriminated in non-immediate hypersensitivity reactions, that is, contact dermatitis (32, 100) and generalized maculopapular rash (101). Of note, the vast majority of patients with proven sensitization to thimerosal as demonstrated by positive patch tests tolerate thimerosal-containing vaccines uneventfully (35, 102–104). However, if possible, alternative vaccines not containing this preservative should be chosen to decrease the risk of local reaction (32, 105). Phenoxyethanol and formaldehyde have increasingly been added to cosmetics and pharmaceuticals, including many vaccines. These preservatives have been rarely incriminated in hypersensitivity reactions to vaccines, those being mainly non-immediate reactions (i.e. contact dermatitis) (34, 36, 106, 107).

Other potentially allergenic vaccine components

Latex

Latex proteins may be present in the environment during the administration of a vaccine (gloves, stoppers, etc.), raising the potential risk of anaphylactic reactions in patients with known allergy to latex. Regarding the stoppers containing latex, the contamination can occur either by physical contact of the liquid vaccine with the stopper, or by passing the needle throughout the stopper, and by retaining latex allergens in or on the needle (108). Although latex as a cause of reaction to vaccine appears to be rare (109), precautions must be taken if a patient has a confirmed allergy to latex, and vaccines from vials with non-latex stoppers should be preferred. If the only available preparation has a latex stopper or contains latex in the packaging, the vaccine can still be administered with caution, that is, avoid passing the needle through the stopper and observation of the patients for at least 30 min. Patients with contact allergy to latex can safely receive vaccines potentially containing latex proteins.

Antibiotics

Some vaccines (i.e. polio, MMR, and influenza vaccines) may contain traces of antibiotics (i.e. neomycin, gentamicin, polymyxin B, and streptomycin) used for viral culture to avoid bacterial and fungal contamination during the manufacturing process. Although these antibiotics in vaccines theoretically could cause anaphylactic reactions, there is no report of confirmed immediate hypersensitivity reactions in the literature. Nevertheless, the few patients who have a confirmed immediate allergy to one of these antibiotics should not receive vaccines containing them (110). These antibiotics, particularly neomycin, are more likely to be responsible for non-immediate hypersensitivity reactions (i.e. contact dermatitis) (111). In this case, (re)vaccination is not strictly contraindicated. As there is a low amount of neomycin found in vaccines, affected patients may develop only a mild local reaction that does not outweigh the benefits of the vaccination (112).

Yeast

Hepatitis B and human papillomavirus vaccines are manufactured using recombinant strains of *Saccharomyces cerevisiae* (common bakers' yeast) and contain residual yeast proteins (110). Large studies on vaccines safety have shown that adverse reactions to these appear to be sporadic (113, 114). Nevertheless, in the rare patients with a positive history of clinical reactivity to Baker's or Brewer's yeast and sensitized to *Saccharomyces cerevisiae*, skin tests with yeast-containing vaccines should be carried out prior to administration (12). In case of positive results, the vaccine can still be administered, but in graded doses.

Milk

Diphtheria/tetanus vaccines are prepared in a medium derived from cow's milk proteins and nanoquantities of residual casein have been demonstrated in these preparations. A recent case

series raised the possibility that residual casein could be responsible for anaphylactic reactions to the diphtheria/tetanus vaccines in patients with severe milk allergy and high level of cow's milk specific IgE (115). The results of this report have been questioned and require confirmation (116). Recently, milk was also incriminated in allergic reaction to Sabin vaccine containing α -lactalbumin, but these data too need to be confirmed by further studies (117).

Dextran

This component has been implicated in severe immediate reactions to BCG, particularly during the neonatal period (118), and to some MMR vaccines (119). From a pathophysiological point of view, the reactions were related to the presence of IgG antibodies to dextran, and it was hypothesized that complement activation and anaphylatoxin release were the main mechanisms. MMR vaccines containing dextran have now been withdrawn from the market, but dextran can be found in other vaccine, that is, in some rotavirus vaccines. Non-immediate reactions to dextran are rare, with exceptional maculopapular exanthema, erythema nodosum, urticarial vasculitis, and neutrophilic dermatoses (Sweet's syndrome, pyoderma gangrenosum) (82, 97).

Management of children with a suspicion of hypersensitivity to vaccine

The diagnosis of vaccine allergy is based on the clinical history, *in vivo* tests (i.e. skin tests) and *in vitro* tests (i.e. specific IgE). No single investigation alone is sufficiently predictive, and a stepwise approach, similar to those for other allergic disorders, is recommended (120, 121). The evaluation will differ according to the vaccine/components involved and the mechanisms suspected. Based on the results of these tests, (re)vaccination is

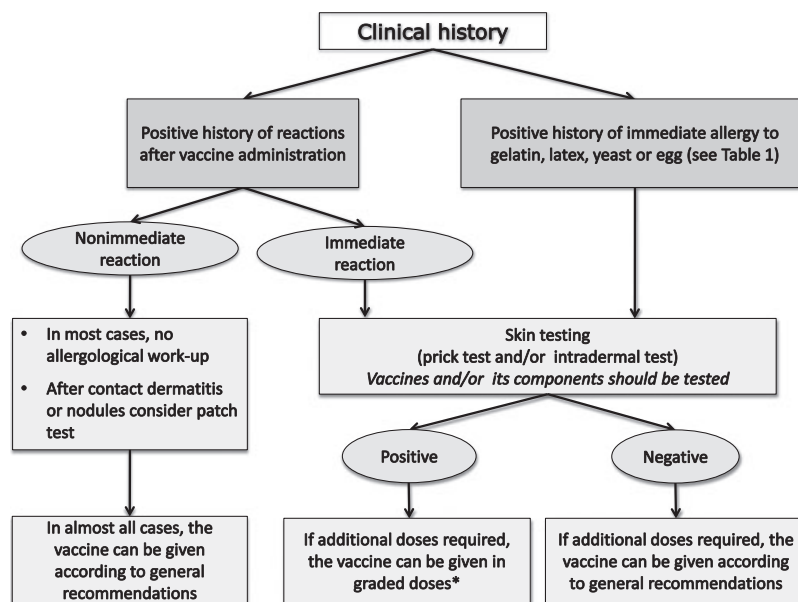
possible in most cases, using adapted protocols if necessary. The management of children with a suspicion of hypersensitivity to vaccine is illustrated in Fig. 1.

Clinical history

The diagnostic workup of suspected vaccine allergy should always start with a detailed history. The primary purpose of the clinical history is to characterize the reaction and to exclude adverse reactions due to intrinsic property of vaccines, to program errors as well as coincidental reactions (11). It is then important to determine the type of hypersensitivity reaction the child likely experienced, particularly by noting the presenting symptoms (i.e. extent and severity of the reaction) and the timing of symptoms in relation to the vaccine administration (i.e. immediate vs. non-immediate). Assessing the ingredients of the incriminated vaccine will help to identify potential allergen (s). Finally, it is extremely important to search for a history of similar reactions to the same vaccine or other vaccines or to vaccines constituents (i.e. egg, latex, gelatin, and yeast).

The diagnosis of 'allergy' is often improperly evoked in patients experiencing a local reaction after vaccine administration. Local reactions should not be considered as a reason for avoiding (re)vaccination (12, 122). These reactions can be treated with cool packs if symptoms are time limited, and/or analgesic drugs if pain or swelling is troublesome. However, these medications may reduce the immune response to vaccination and should not be administered empirically or prophylactically (123). It is sometimes difficult to distinguish these reactions clinically from an infectious cellulitis. Local inflammatory reactions are relatively common after vaccine administration, whereas injection-related bacterial cellulitis is quite rare and appears with some delay. Minimal local tenderness and absence of systemic signs of toxicity should orientate the diagnosis to a benign local reaction and lead to clinical

Figure 1 Management of patients with suspected hypersensitivity to a vaccine and of patients with known allergy to a vaccine component.
*For a vaccine dose of 0.5 ml (standard dose), administer graded doses of vaccine at 15-min intervals: 0.05 ml of 1:10 dilution, 0.05 ml of full strength, 0.1 ml of full strength, 0.15 ml of full strength, and 0.2 ml of full strength.



observation of the patients, thus avoiding unnecessary antibiotic treatment. Nevertheless, to avoid missing an instance of bacterial cellulitis at an early stage, it is important to closely monitor the patient and to assess for any unexpected progression in fever, toxicity, or lesional discomfort (124).

Regarding systemic reactions, the first step is to determine whether the nature and timing of the reaction are consistent with an IgE-mediated reaction. An immediate reaction manifests by various combinations of IgE-mediated symptoms, that is, urticaria and/or angioedema, rhinitis, wheezing, and hypotension. Nevertheless, the distinction between a real allergy and a non-specific reaction is often difficult, especially for cutaneous reactions as they can be caused by many cofactors, especially intercurrent infections. From another point of view, vasovagal attacks associated with injections are common and must be distinguished from an anaphylaxis (122, 125). Serum tryptase measurement 1–8 h after the suspected anaphylaxis can be useful. Other causes of allergy should also be excluded, particularly to a food or a drug, as some medications are commonly given concomitantly, particularly NSAID.

Allergological workup

Once a careful clinical history has been obtained, the ratio between risk and therapeutic benefit should be assessed, and the physician should determine whether subsequent doses of the suspected vaccine, or other vaccines with similar components, are required. Measurement of antibodies to the immunizing agent in a vaccine to determine whether they are at protective levels can help determining whether booster injections can be withheld.

However, in case of suspicion of an immediate allergic reaction, the allergological workup should be carried out even if no further doses of the suspected vaccine are required, given the potential for cross-reaction with common components in other vaccines and foods. The assessment will be carried out mainly with allergy skin tests (prick tests and intradermal tests). The vaccine itself as well as the potential single components that may have caused the reaction (i.e. egg, gelatin, latex, and/or *Saccharomyces cerevisiae* yeast) should be tested (12, 52, 126). Regarding skin test with the vaccine itself, the prick method should be used first. If the initial vaccine reaction was life-threatening, it is appropriate to use diluted vaccine for the skin prick test. In all other cases, full-strength vaccine should be used for the skin prick test. If the full-strength skin prick test result is negative, an intradermal test with the vaccine diluted 1:100 should be performed (127). The sensitivity and the specificity are not optimal (68, 128–131), but the main purpose of these tests is to identify patients who are at real risk of developing a severe anaphylactic reaction in case of re-exposure. The allergological workup can be completed by *in vitro* assays for specific IgE, available for egg, gelatin, latex, and yeast.

Following local non-immediate reaction to a vaccine, allergy testing is not required before (re)vaccination. Although patch tests can be helpful to demonstrate a delayed hypersensitivity to preservatives or adjuvants, they are not accurate for the purpose of assessing a patient's ability to tolerate a vaccine. Following contact dermatitis or persistent nodules to a vaccine,

a positive patch test to aluminum, preservatives, or antibiotics may guide clinicians to administer a vaccine free of these components, if available, but is normally no reason to withhold administration of a vaccine following a risk–benefit analysis. In presence of an extensive and painful local reaction, an Arthus reaction should be suspected, and vaccination antibodies should be measured before (re)vaccination (12). The decision to administer an additional dose of vaccine will be based mainly on clinical judgment as local reactions may be uncomfortable but are not associated with a life-threatening risk. Of note, mild generalized urticarial reactions of delayed onset often result from a non-specific degranulation of mast cells and do not contraindicate (re)vaccination. Although controversial, oral antihistamines treatment can be given for 48 h to ensure patient comfort after administration of the vaccine (110, 132).

Vaccine administration according to the results of the allergological workup

- If skin tests are negative, an IgE-mediated allergy to any vaccine constituent is very unlikely and the vaccine can be administered in the usual manner, but the patient should be observed for at least 30 min afterward (12). Of note, some authors still recommend to administer the vaccine in 2 doses (10% followed 30 min later by the remaining 90%) if the patient has a history strongly suggestive of a severe anaphylactic reaction, although there are no reports of patients with negative intradermal skin test to a vaccine reacting to subsequent administration of that vaccine (12, 110, 126).
- If skin tests are positive in a patient with a compatible history of an IgE-mediated reaction, an alternative vaccine not containing the offending component should be favored. If the patient requires additional doses of the suspect vaccine or another vaccine containing the incriminated component, the vaccine will be fractionally according to a predetermined regimen (Fig. 1) as suggested by the American Academy of Pediatrics. In this case, there is a risk of anaphylaxis, and the administration of a vaccine should be performed in a secure environment (trained personnel on-site and emergency drugs available) (126, 133).

Egg-allergic patients and vaccinations

Table 1 illustrates the management of egg-allergic patients who need to receive a vaccine potentially containing egg proteins. Regarding administration of influenza vaccine in egg-allergic patients, recent studies have led to a modification of the management of these patients as described in Table 1 (67). Evaluation of the status of their egg allergy by an allergist is appropriate, although this should not delay their influenza vaccination (12). In patients with egg allergy only, skin testing (skin prick test and/or intradermal test) with influenza vaccine itself does not reliably identify patients with increased risk of reacting to the vaccine and is not recommended (12). However, these tests are appropriate and should be performed in patients with a history of allergic reaction to the influenza vaccine itself.

Patients with a mild egg allergy can receive influenza vaccine in a primary care provider's office, provided the appropriate personnel and equipment are available. In case of severe egg allergy, it is recommended to immunize in an allergist's office (82). Regarding other vaccines containing egg protein, particularly yellow fever, it is still recommended to test the vaccine before administration. In case of positive testing, the vaccine can be administered in graded doses (12, 82).

Conclusion

The diagnosis of allergy to vaccine is complex, and these allergies are often overdiagnosed, mostly due to fear of severe

anaphylaxis. The economic impact and the impact on health, both from an individual point of view and in terms of public health, are very important. Indeed, most of the patients labeled as allergic to a vaccine may tolerate a subsequent injection of the vaccine without clinical reaction. Before this diagnosis can accurately be made, a complete workup is essential. If an allergological workup is required, it will be primarily based on skin tests. In the vast majority of cases, the vaccines can be administered using adapted protocols, even if the skin tests are positive. However, some vaccines' administrations carry a relatively high risk of severe anaphylactic reactions and should always be performed by well-trained physicians, and emergency equipment must be readily available.

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